DETAILED ACTION

Applicant's amendment filed on 1/14/2010 has been entered for the purpose of a compact prosecution. This is because the amendment to the claims does not comply with the requirements of 37 CFR 1.121(c) because **the status of claim 11 should be "Withdrawn" rather "Previously presented"** since claim 11 was withdrawn in the Office action dated 10/14/2009.

Amended claims 1-11 and 20-23 are pending in the present application.

Applicants elected previously the following species: (a) a gemini cationic surfactant; (b) a cream and (c) DOPE.

Claims 11 and 20-23 were withdrawn previously from further consideration because they are directed to non-elected invention and non-elected species.

Accordingly, amended claims 1-10 are examined on the merits herein with the above elected species.

Response to Amendment

The provisional rejection on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-38 of copending Application No. 12/215,963 was withdrawn in light of Applicant's amendment.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Amended claims 1-4 and 6-10 are rejected under 35 U.S.C. 102(b) as being anticipated by Camilleri et al (WO 99/29712; IDS). ***This is a modified rejection necessitated by Applicant's amendment.***

Camilleri et al (WO 99/29712; IDS) already disclose at least a mixture of peptide-based Gemini compounds and polynucleotides (e.g., DNA, RNA and plasmid vector) for gene therapy and genetic immunization in whole organisms as well for transfection of polynucleotides in cells in culture, **wherein the Germini compounds have a linker group Y, preferably $(CH_2)_m$ where m is an integer from 1 to 6** (pages 2-6; particularly page 3, lines 19-20; and examples 17-19). The peptide-based Gemini compounds comprise positively charged hydrophilic heads and hydrophophic tails of C(10-20) saturated or unsaturated alkyl groups (see at least page 2, line 15 continues to line 7 of page 5). Camilleri et al further disclose specifically that the gemini compound may be used in combination with one or more supplements to increase the efficiency of transfection, and the supplements include a neutral carrier such as dioleyl phosphatidylethanolamine or DOPE (page 5, lines 21-26). In exemplifications, such mixtures comprising of peptide-based Gemini compounds and polynucleotides are in a serum-free solution medium (see at least examples 17-19).

Since the mixtures of Camilleri et al have at least the same components and form as a topical delivery system as broadly written and claimed, the teachings of Camilleri et al meet every limitation of the instant claims.

Additionally, please, also note that where, as here, the claimed and prior art products are identical **or** substantially identical, **or** are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. See In re Ludtke. Whether the rejection is based on "inherency" under 35 USC 102, or "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. In re Best, Bolton, and Shaw, 195 USPQ 430, 433 (CCPA 1977) citing In re Brown, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972).

Accordingly, the reference anticipates the instant claims.

Response to Arguments

Applicants' arguments related to the above rejection in the Amendment filed on 1/14/2010 (pages 4-6) have been fully considered but they are respectfully not found persuasive for the reasons discussed below.

Applicants argue basically that the Gemini surfactants described by Camilleri are not the same as the Gemini surfactant in the claimed topical delivery system, and therefore the reference does not anticipate the instant claims. Additionally, Applicants

argue that Camilleri is silent with respect to topical or transdermal delivery of a nucleic acid nor that a topical delivery system could provide a therapeutic effect; and therefore the above rejection should be withdrawn.

First, **the mixtures of Camilleri et al have at least the same components and form as a topical delivery system as broadly written and claimed for the reasons set forth above,** therefore the teachings of Camilleri et al meet every limitation of the instant claims. Please note that Camilleri et al teach explicitly that **the Germini compounds have a linker group Y, preferably $(CH_2)_m$ where m is an integer from 1 to 6.**

Second, it appears that Applicants read a narrow embodiment of the specification into the claims. This is because **the instant claims do not necessarily limit to a gemini surfactant having the formula shown in Fig. 1 or in Table 1**. Moreover, please note that as defined by the instant specification on page 4, lines 16-17; the term "Gemini surfactant" means a surfactant molecule which contains more than one hydrophobic tail.

Third, it should also be noted that for a composition claim its intended use is not given any patentable weight in light of the prior art. For this instance, the limitation "when in contact with skin or a mucosal membrane, provides a therapeutic effect" is an intended use. Nevertheless, as already explained in details in the above rejection **the mixtures of Camilleri et al have at least the same components and form; and are indistinguishable from a topical delivery system as broadly claimed.**

Amended claims 1-4 and 6-10 are rejected under 35 U.S.C. 102(e) as being anticipated by Wheeler, C (US 6,696,424). ***This is a modified rejection necessitated by Applicant's amendment.***

Wheeler already teaches a composition comprising a novel cationic lipid compound having hydrophobic tails and two quarternary ammonium headgroups bridged by a linker that is useful for facilitating delivery and transfection of biologically active agents such as DNA (e.g., plasmid DNA) into cells (see at least Summary of the Invention and the abstract). The cationic lipid compounds have general formula (I) and (II), with R1, R2, R3 and R4 are C1 to C24 alkyl or alkenyl; and R5, R6, R7 and R8 are C1 to C10 alkyl or alkenyl (see col. 6; col. 8; and Figures 1A-1B). **It is noted that the compounds having the general formula (I) and (II) contain the moieties (CH2)n and (CH2)m, wherein n and m are the same or different and are 1 to 8 (col. 6, lines 45-67; col. 8, lines 19-47); and that these moieties could be considered to be "spacers". Additionally or alternatively the compounds having the general formula (I) and (II) have the R9 component that can be at least substituted C1 to C10 alkyl; with exemplified compounds shown in Fig. 1A and 1B contain at least $(CH_2)_3$ as denoted by a zigzag line connecting the 2 quarternary N+ head groups**. Accordingly, these cationic lipid compounds fall within the scope of a gemini cationic surfactant as broadly claimed; and please note that the term "Gemini surfactant" means a surfactant molecule which contains more than one hydrophobic tail as defined by the instant specification on page 4, lines 16-17. Wheeler also disclose an immunogenic composition comprising a nucleotide sequence that encodes an immunogen (one or

more multiple plasmids) and the composition comprising a novel cationic lipid compound having hydrophobic tails and two quarternary ammonium headgroups bridged by a linker to treat viral, bacterial, fungal and parasitic infectious diseases; and the immunogenic composition further includes one or more co-lipids or other lipid aggregate-forming components such as phospholipids, lysophopholipids, lyso lipids and cholesterol (col. 3, line 44 continues to line 19 of col. 4; col. 11, lines 55-59). Moreover, the immunogenic composition can also be **in the form of topical skin creams** (see at least col. 14, line 44 continues to line 16 of col. 17).

Since the immunogenic composition of Wheeler has the same components and form as a topical delivery system as broadly written and claimed, the teachings of Wheeler meet every limitation of the instant claims.

Additionally, please, also note that where, as here, the claimed and prior art products are identical **or** substantially identical, **or** are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. See In re Ludtke. Whether the rejection is based on "inherency" under 35 USC 102, or "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. In re Best, Bolton, and Shaw, 195 USPQ 430, 433 (CCPA 1977) citing In re Brown, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972).

Accordingly, the reference anticipates the instant claims.

Response to Arguments

Applicants' arguments related to the above rejection in the Amendment filed on 1/14/2010 (pages 7-8) have been fully considered but they are respectfully not found persuasive for the reasons discussed below.

Applicants argue basically that Wheeler describes thousands of possible germini surfactants, and there is no guidance in Wheeler's listing from which a skilled artisan would arrive at Gemini surfactants having a spacer with a length corresponding to (CH2)n, where n is 3, 4, 6 or 16. Additionally, there is no showing in Wheeler of which, and if any, Gemini surfactant would provide for topical delivery of a nucleic acid in sufficient amounts for a therapeutic effect.

First, the immunogenic composition of Wheeler has the same components and form, and it is indistinguishable from a topical delivery system as broadly claimed. Particularly, **as already noted in the above rejection that the compounds having the general formula (I) and (II) contain the moieties (CH2)n and (CH2)m, wherein n and m are the same or different and are 1 to 8 (col. 6, lines 45-67; col. 8, lines 19-47); and that these moieties could be considered to be "spacers". Additionally or alternatively the compounds having the general formula (I) and (II) have the R9 component that can be at least substituted C1 to C10 alkyl; with exemplified compounds shown in Fig. 1A and 1B contain at least $(CH_2)_3$ as denoted by a zigzag line connecting the 2 quarternary N+ head groups**. Accordingly, these cationic lipid compounds fall within the scope of a gemini cationic surfactant as broadly

claimed; and please also note that as defined by the instant specification on page 4, lines 16-17; the term "Gemini surfactant" means a surfactant molecule which contains more than one hydrophobic tail.

Second, it appears that Applicants read a narrow embodiment of the specification into the claims. This is because **the instant claims do not necessarily limit to a gemini surfactant having the formula shown in Fig. 1 or in Table 1**.

Third, it should also be noted that for a composition claim its intended use is not given any patentable weight in light of the prior art. For this instance, the limitation "when in contact with skin or a mucosal membrane, provides a therapeutic effect" is an intended use. Nevertheless, as already explained in details in the above rejection **the immunogenic composition of Wheeler has at least the same components and form; and it is indistinguishable from a topical delivery system as broadly claimed.**

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Amended claims 1, 4 and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Camilleri et al (WO 99/29712; IDS) or Wheeler (US 6,696,424) in view of Weiner et al (US 5,981,505). ***This is a modified rejection necessitated by Applicant's amendment.***

Camilleri et al (WO 99/29712; IDS) already disclose at least a mixture of peptide-based Gemini compounds and polynucleotides (e.g., DNA, RNA and plasmid vector) for gene therapy and genetic immunization in whole organisms as well for transfection of polynucleotides in cells in culture, **wherein the Germini compounds have a linker group Y, preferably $(CH_2)_m$ where m is an integer from 1 to 6** (pages 2-6; particularly page 3, lines 19-20; and examples 17-19). The peptide-based Gemini compounds comprise positively charged hydrophilic heads and hydrophophic tails of C(10-20) saturated or unsaturated alkyl groups (see at least page 2, line 15 continues to line 7 of page 5). Camilleri et al further disclose specifically that the gemini compound may be used in combination with one or more supplements to increase the efficiency of transfection, and the supplements include a neutral carrier such as dioleyl phosphatidylethanolamine or DOPE (page 5, lines 21-26). In exemplifications, such mixtures comprising of peptide-based Gemini compounds and polynucleotides are in a

serum-free solution medium (see at least examples 17-19). It is noted that the mixtures of Camilleri et al have at least the same components and form as a topical delivery system as broadly written and claimed.

Wheeler already teaches a composition comprising a novel cationic lipid compound having hydrophobic tails and two quarternary ammonium headgroups bridged by a linker that is useful for facilitating delivery and transfection of biologically active agents such as DNA (e.g., plasmid DNA) into cells (see at least Summary of the Invention and the abstract). The cationic lipid compounds have general formula (I) and (II), with R1, R2, R3 and R4 are C1 to C24 alkyl or alkenyl; and R5, R6, R7 and R8 are C1 to C10 alkyl or alkenyl (see col. 6; col. 8; and Figures 1A-1B). **It is noted that the compounds having the general formula (I) and (II) contain the moieties (CH2)n and (CH2)m, wherein n and m are the same or different and are 1 to 8 (col. 6, lines 45-67; col. 8, lines 19-47); and that these moieties could be considered to be "spacers". Additionally or alternatively the compounds having the general formula (I) and (II) have the R9 component that can be at least substituted C1 to C10 alkyl; with exemplified compounds shown in Fig. 1A and 1B contain at least $(CH_2)_3$ as denoted by a zigzag line connecting the 2 quarternary N+ head groups**. Accordingly, these cationic lipid compounds fall within the scope of a gemini cationic surfactant; of the claims and please note that the term "Gemini surfactant" means a surfactant molecule which contains more than one hydrophobic tail as defined by the instant specification on page 4, lines 16-17. Wheeler also disclose an immunogenic composition comprising a nucleotide sequence that encodes an immunogen (one or

more multiple plasmids) and the composition comprising a novel cationic lipid compound having hydrophobic tails and two quarternary ammonium headgroups bridged by a linker to treat viral, bacterial, fungal and parasitic infectious diseases; and the immunogenic composition further includes one or more co-lipids or other lipid aggregate-forming components such as phospholipids, lysophopholipids, lyso lipids and cholesterol (col. 3, line 44 continues to line 19 of col. 4; col. 11, lines 55-59). Moreover, the immunogenic composition can also be **in the form of topical skin creams** (see at least col. 14, line 44 continues to line 16 of col. 17). Once again, the immunogenic composition of Wheeler has the same components and form as a topical delivery system as broadly written and claimed.

However, neither Camilleri et al nor Wheeler teach specifically a composition comprising a plasmid vector comprising a gene coding for interferon-γ.

However, at the effective filing date of the present application Weiner et al already taught at least an immunogenic composition comprising nucleotide sequences that encode a target protein and further include genes for proteins that enhance the immune response against such target proteins; and examples of such genes include those which encode interferon-γ, GM-CSF, IL-2, IL-12 (see at least Summary of the Invention and particularly col. 7, lines 54-65)..

Accordingly, it would have been obvious for an ordinary skilled artisan to modify the composition of either Camilleri et al or Wheeler by also including a plasmid vector construct comprising a gene coding for interferon-γ in light of the teachings of Weiner et al.

An ordinary skilled artisan would have been motivated to carry out the above modification because Weiner et al already taught specifically that the further inclusion of genes such as those which encode interferon-γ, GM-CSF, IL-2, IL-12 in an immunogenic composition to enhance the immune response against targeted proteins. Furthermore, both Camilleri et al and Wheeler teach at least a composition that is suitable for gene therapy and genetic immunization.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of either Camilleri et al or Wheeler and Weiner et al., coupled with a high level of skill for an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

Applicants' arguments related to the above rejection in the Amendment filed on 1/14/2010 (pages 9-10) have been fully considered but they are respectfully not found persuasive for the reasons discussed below.

Applicants argue basically that Wheeler does not show or suggest a topical delivery system comprised of a Gemini surfactant as claimed; and does not mention Gemini surfactants. Therefore, the combined teachings of Wheeler and Weiner fail to show or suggest each and every claimed element or a reasonable expectation of success in achieving a therapeutic response upon topical application of the claimed delivery system. Furthermore, Applicants argue that the claimed delivery system

produces an unexpected result because as shown in Table 1, on page 27 of the present application, delivery systems with a Gemini surfactant having a spacer with a length corresponding to (CH2)n, where n is 3, 4, 6 or 16 provide significantly higher levels of transfection than delivery systems comprised of a gemini surfactant with other spacer lengths, and this result could not be known or predicted based on the combined teachings of the cited art.

First, please refer to the Examiner's same responses to Applicants' alleged deficiency of Wheeler's teachings in the rejection of claims 1-4 and 6-10 under 35 U.S.C. 102(e) as being anticipated by Wheeler, C (US 6,696,424) above.

Second, once again **the instant claims do not necessarily limit to a gemini surfactant having the formula shown in Fig. 1 or in Table 1 or any particular compound listed in Table 1**. The alleged "unexpected result" **is merely a significantly higher IFNgamma levels when cultured cells were transfected with 12-3-12, 12-4-12 and 16-3-16 versus other tested compounds with longer linkers such as 12-6-12 and 12-16-12 compounds** (see page 27 and Table 1). Nevertheless, the composition of either Camilleri et al or Wheeler contains a spacer that meets the recited limitation. Thus, there is nothing that is unexpected or any rationale why the combined teachings of either Camilleri et al or Wheeler in view of Weiner et al would not have any reasonable expectation of success for a topical delivery system as broadly claimed.

Third, the main purpose for the citation of the Weiner et al reference is to supplement either the teachings of Camilleri et al or Wheeler on the specific use of a

plasmid vector containing the IFNgamma gene (limitation of claim 5). As already set forth in the above rejection, it would have been obvious for an ordinary skilled artisan to modify the composition of either Camilleri et al or Wheeler by also including a plasmid vector construct comprising a gene coding for interferon-γ because Weiner et al already taught specifically that the further inclusion of genes such as those which encode interferon-γ, GM-CSF, IL-2, IL-12 in an immunogenic composition to enhance the immune response against targeted proteins. Furthermore, both Camilleri et al and Wheeler teach at least a composition that is suitable for gene therapy and genetic immunization.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Chu et al (WO 00/27795; IDS) also taught compounds capable of facilitating transport of biologically active agents or substances, including nucleic acids, into cells having general structure (A), where the linking component L can be (CH2)l with l is from 0 to about 100; and the compounds can be used in combination with other lipid aggregate-forming components such as DOPE (see at least Summary of the Invention).

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's SPE, Joseph T. Woitach, Ph.D., may be reached at (571) 272-0739.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It

also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

/QUANG NGUYEN/
Primary Examiner, Art Unit 1633